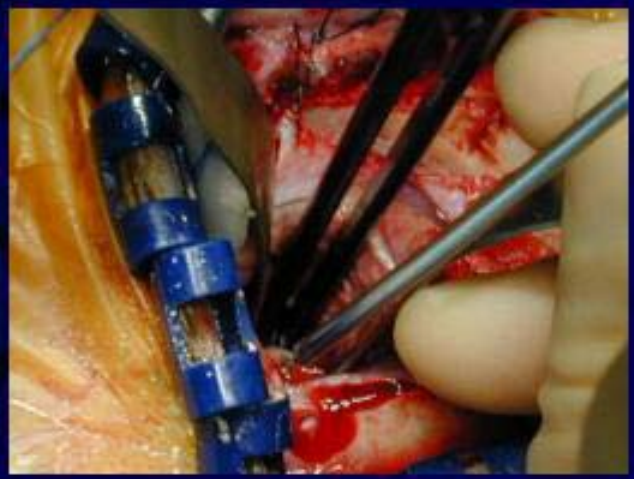
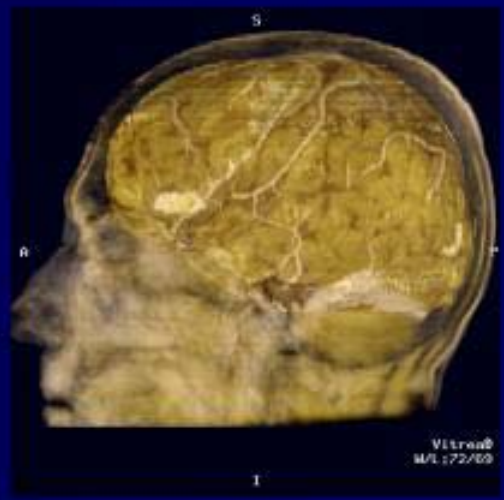
Integrated Image Guided Diagnosis and Therapy

Timothy Ryken, MD





Brain Tumor Treatment Group

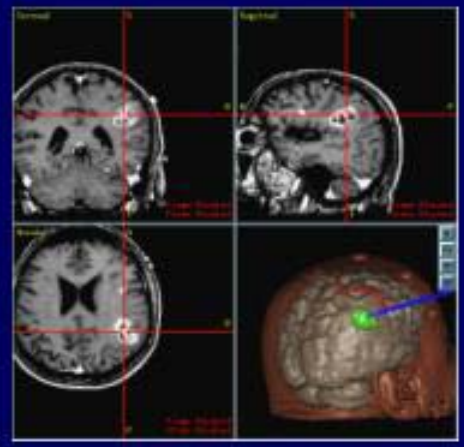
Molecular Neurosurgery Laboratory

Department of Neurosurgery

Holden Comprehensive Clinical Cancer Center

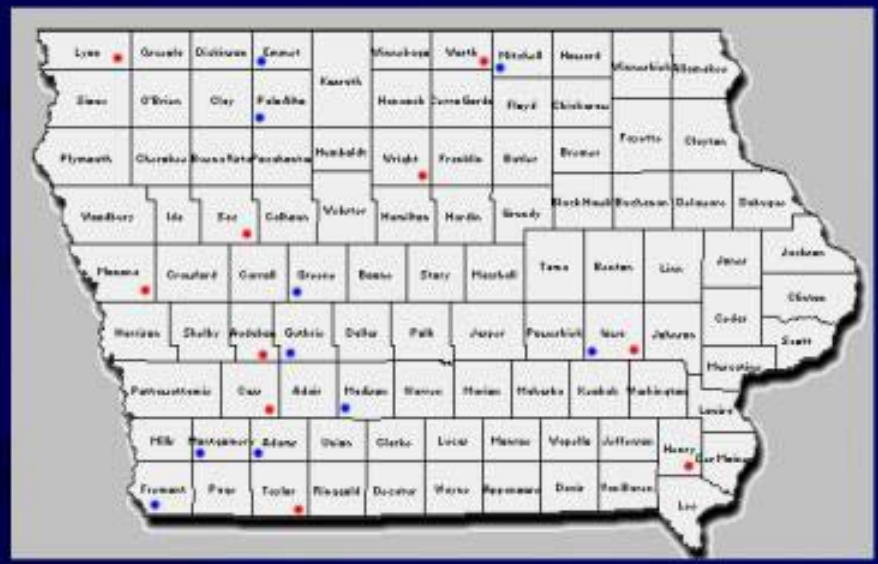
University of Iowa Hospitals and Clinics

Primary Malignant Brain Tumors



15,000 to 20,000 per year (USA)

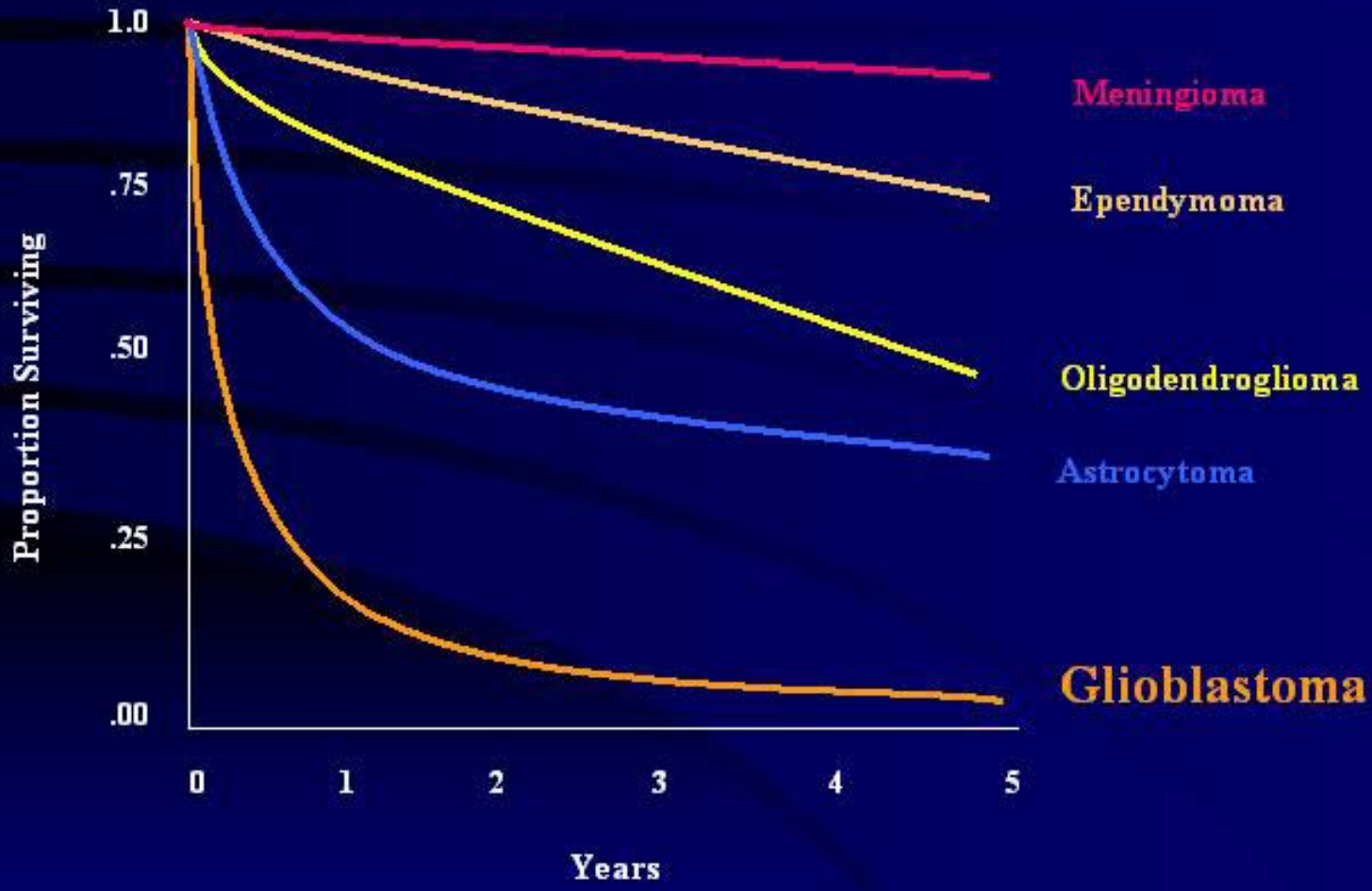
(Iowa 250 per year)



Malignant Glioma Incidence (per capita by county)
Red – Top Ten 1974-1985 Blue – Top Ten 1984-1995

1884

Primary Glial Tumors: General Survival Trends



Patient presents with CNS disease

Diagnostic Neuroimaging

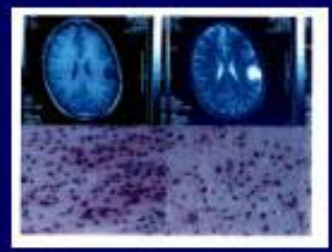
Image Guidance

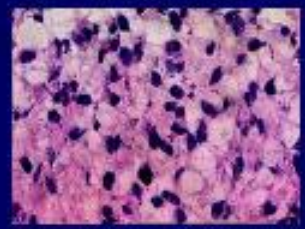
Diagnostic Procedure

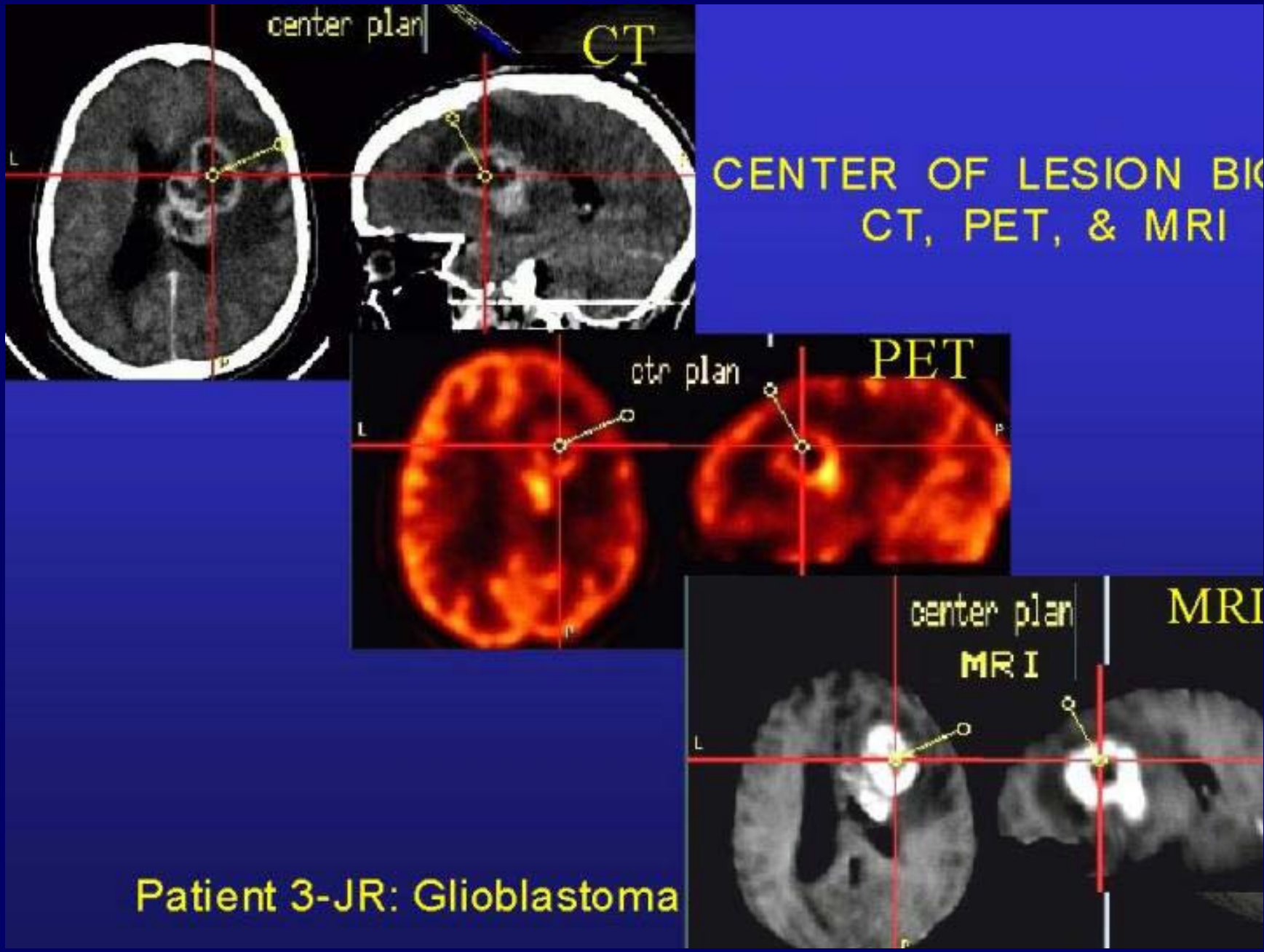
Pathologic Diagnosis

Treatment

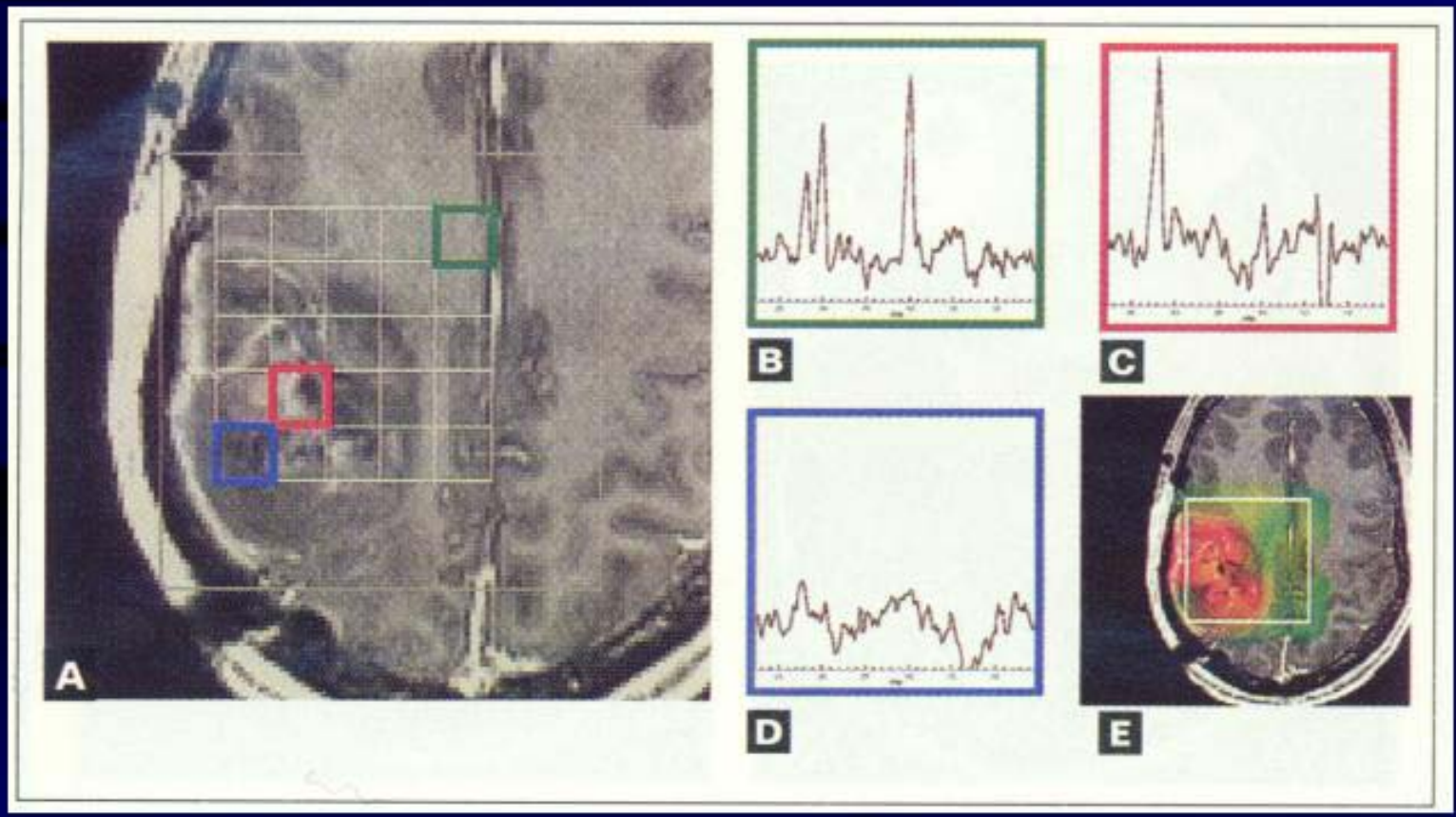
1995



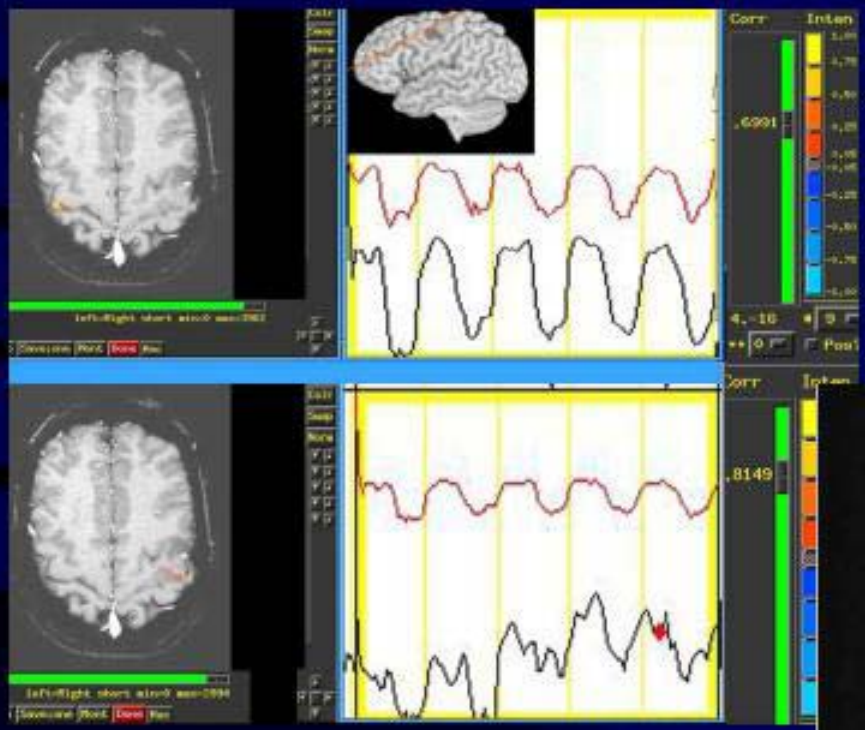


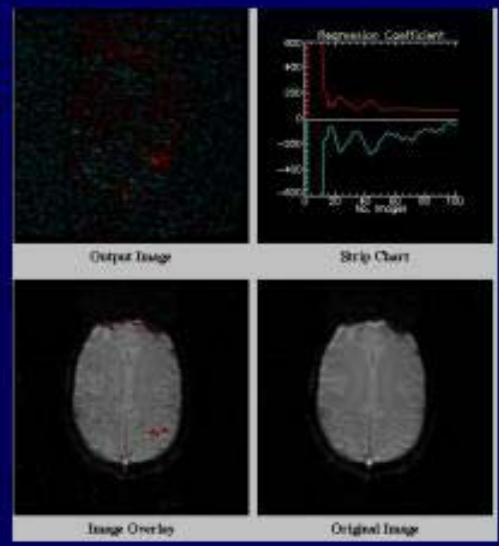

center plan
CT
CENTER OF LESION BIO
CT, PET, & MRI
ctr plan
PET
center plan
MRI
MRI
Patient 3-JR: Glioblastoma

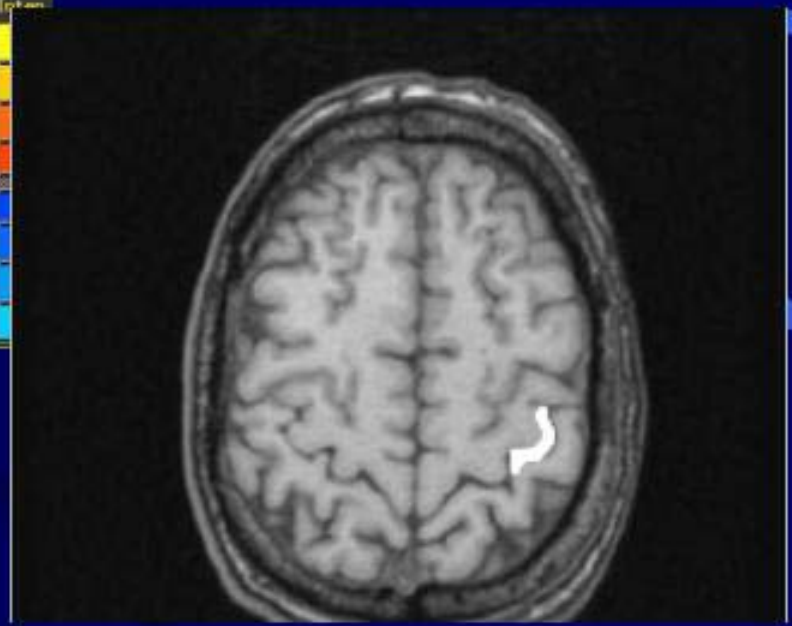
Imaging: Magnetic Resonance Spectroscopy



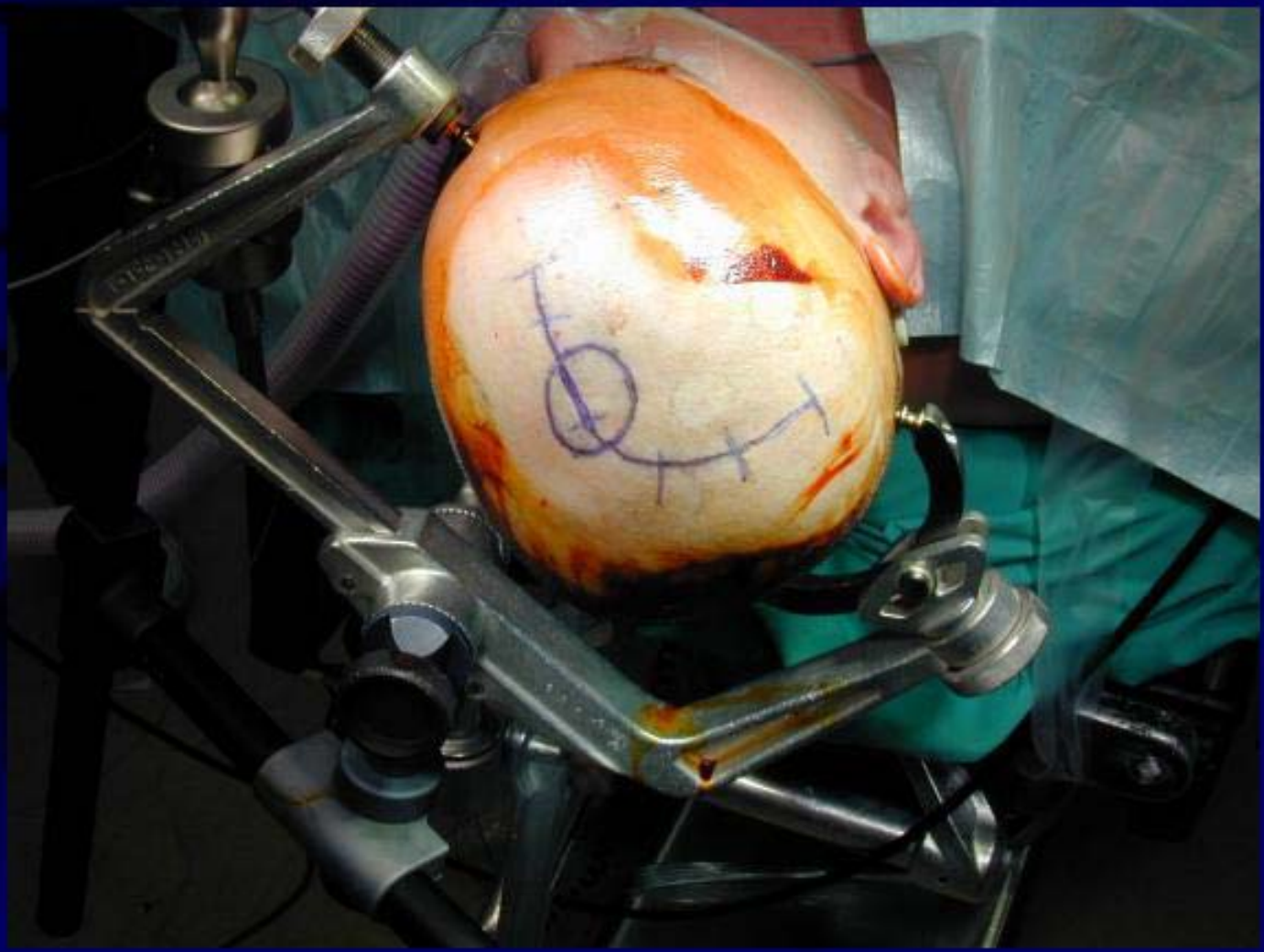
MRI – Functional Mapping







(Whoops !)



Patient presents with CNS disease

Multimodality Neuroimaging

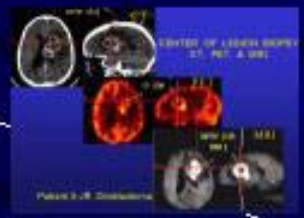
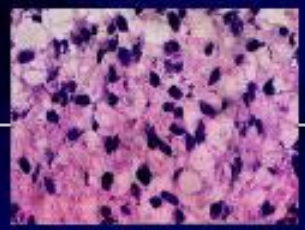


Image Guided Surgical Platform

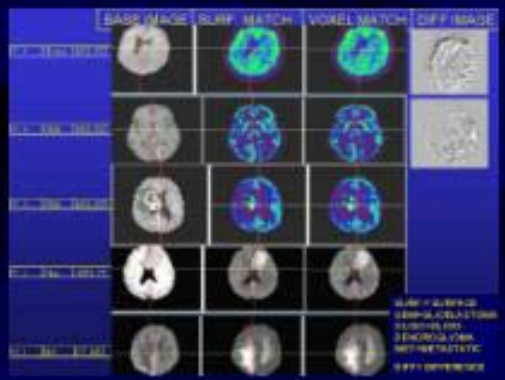
"Tailored" Diagnostic Procedure

Pathologic Diagnosis



Treatment
Based on histochemistry or limited genetic testing

2002



Need for:

Clinician-friendly tools for integration of multimodality images

Multi-modality Imaging

Preoperative planning

Anatomical based trajectories

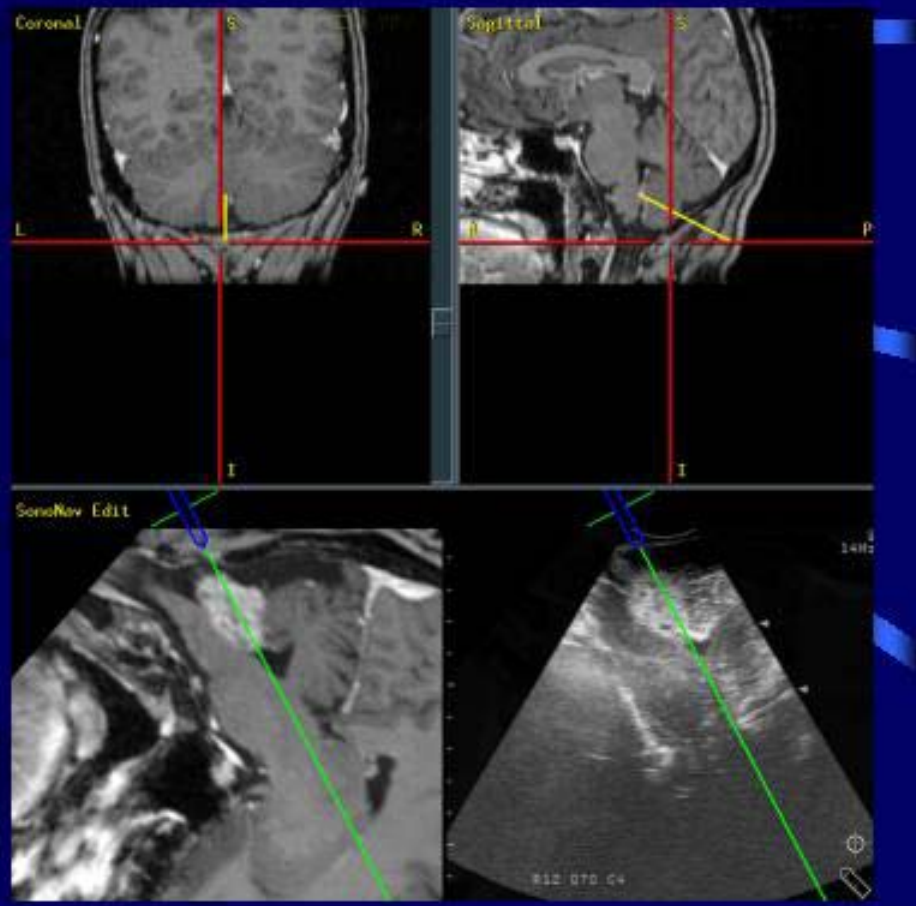
Advanced trajectories
Functional MRI
Electrocorticography
MR spectroscopy
PET
Target selection (multi-modality)

Image-guided Neurosurgical Treatment Platforms

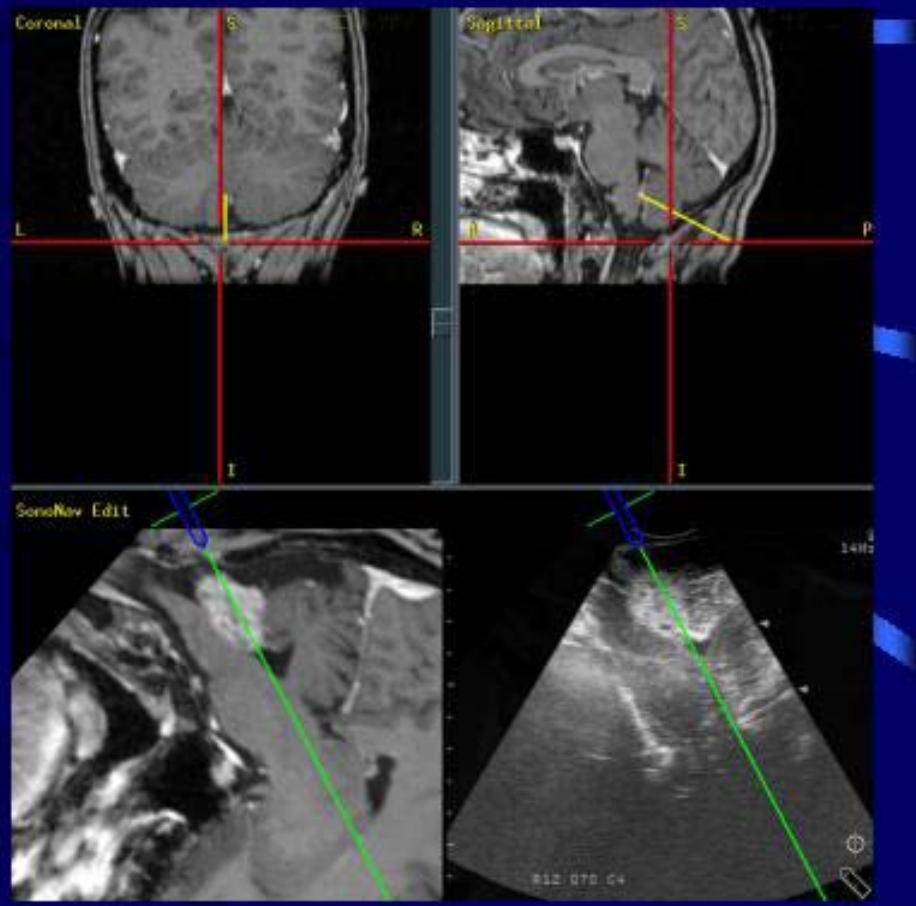
University of Iowa

(circa – 2001)

Ultrasound-linked image guided navigation

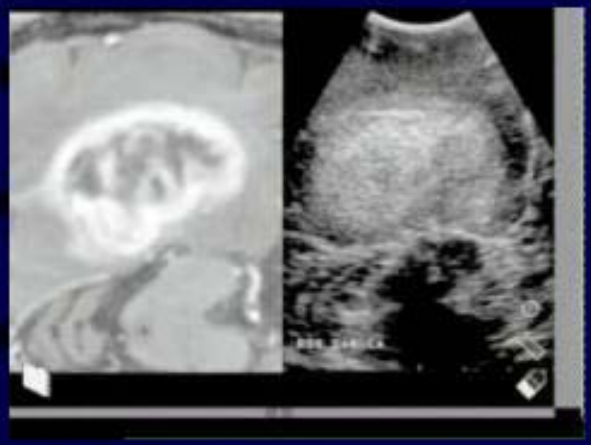


Ultrasound-linked image guided navigation



Ultrasound-linked image guided navigation

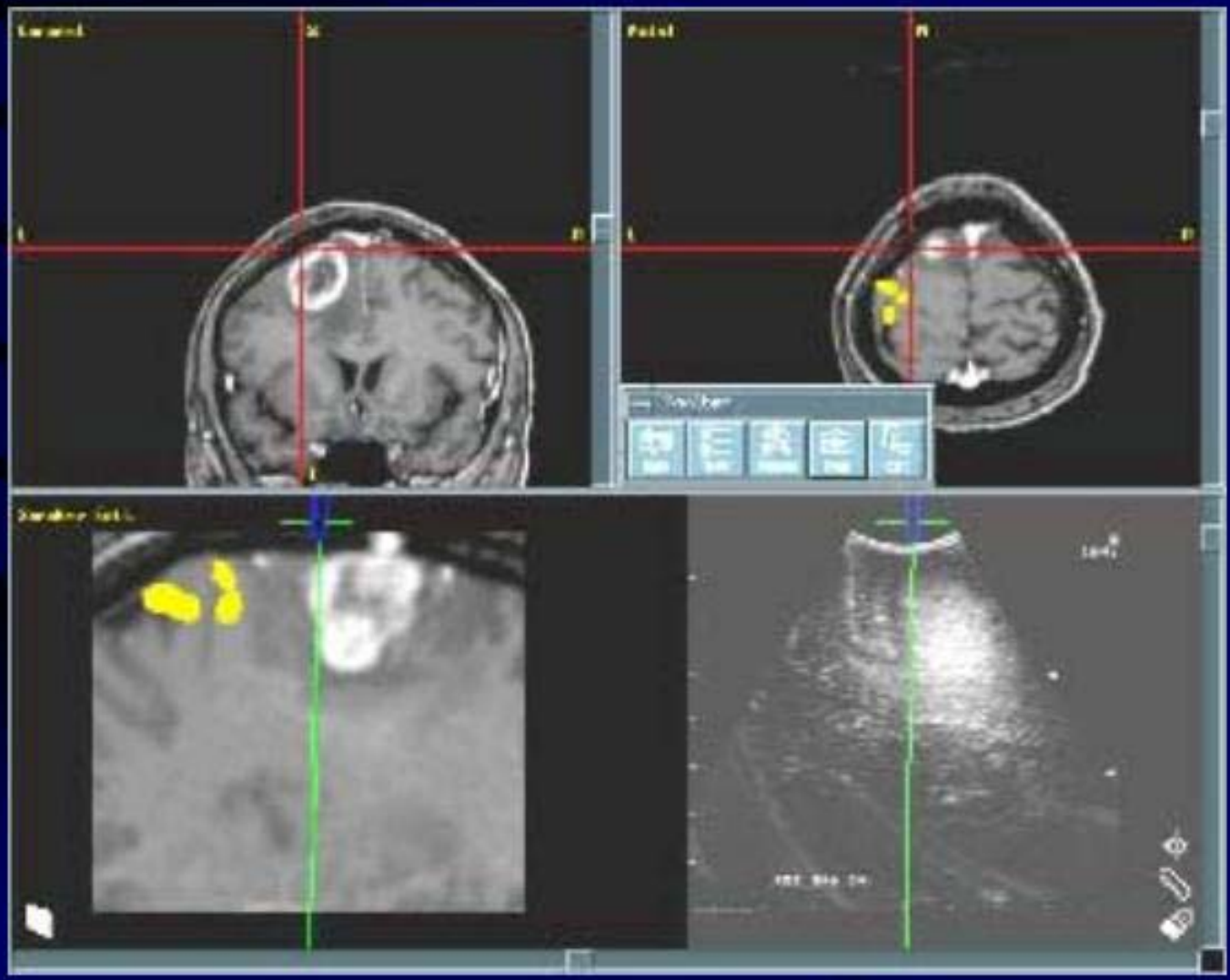
Pre-resection assessment

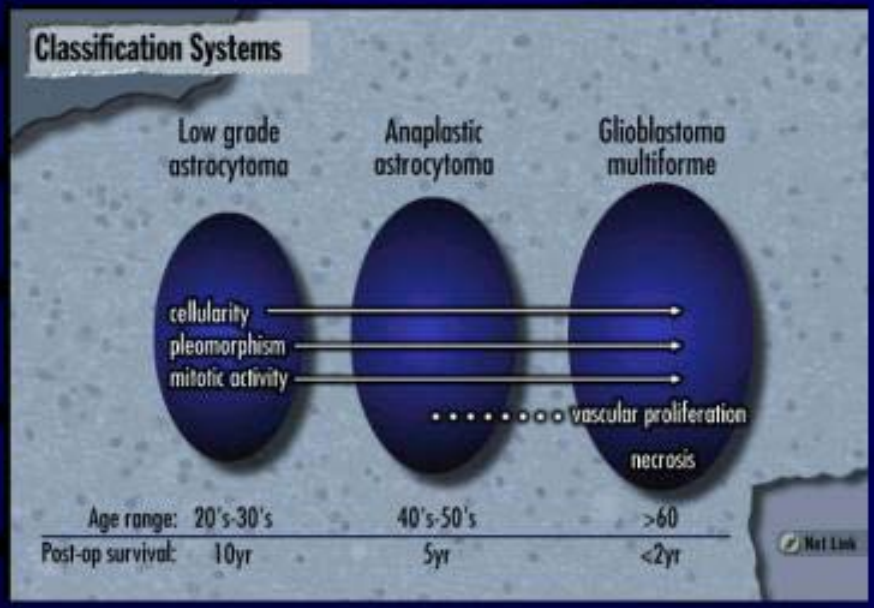


Intraoperative shift

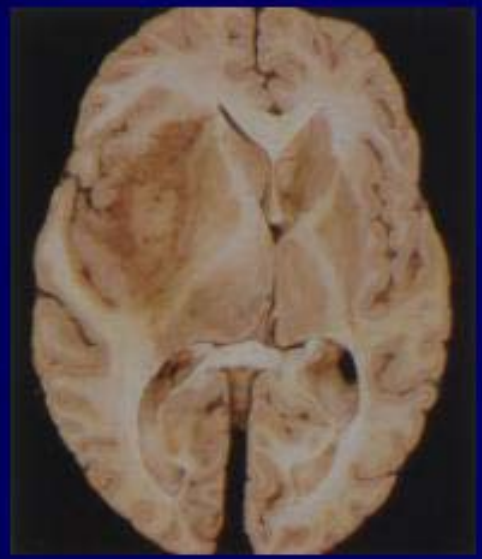
Resection assessment

Image fusion – fMRI, MRI, US

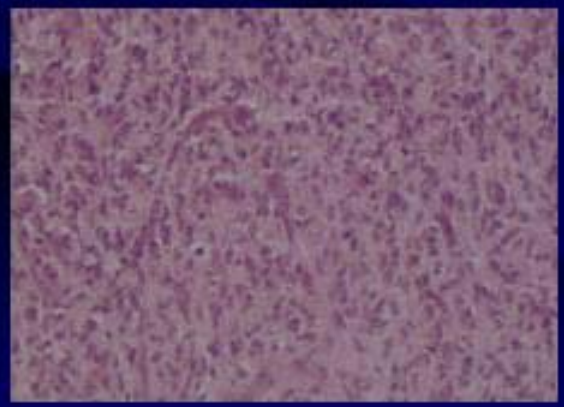




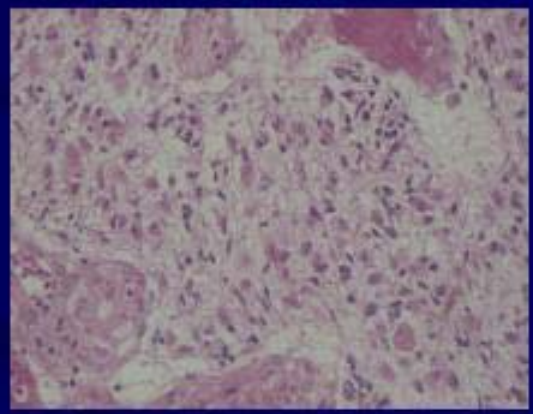
Gross Pathology:



Histopathology:



Anaplastic Astrocytoma

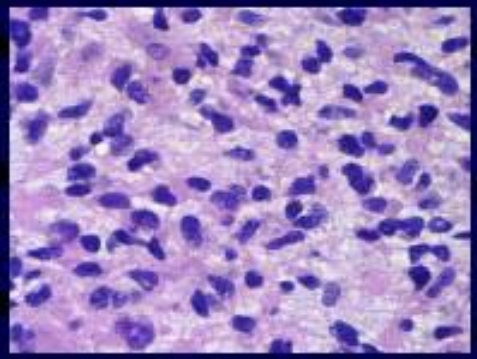


Glioblastoma

X-Cyt Project

(Nick Street, Ph.D. – University of Iowa)

Digitized Image



Segmented Cell Nuclei

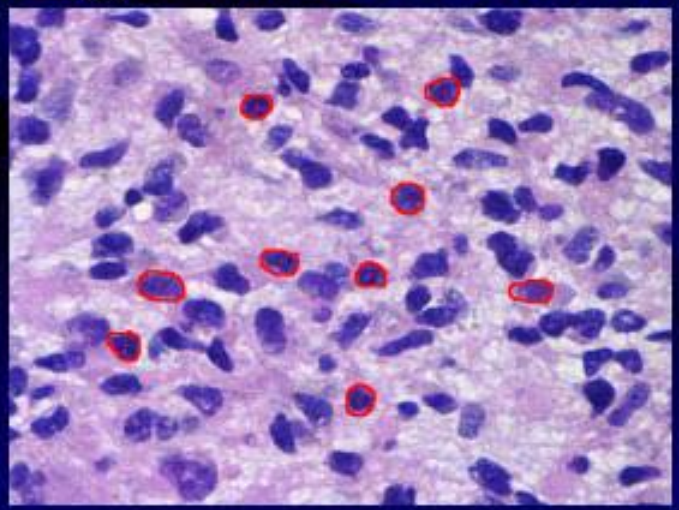


Image Analysis

TABLE 1. DIAGNOSTIC FEATURES

	BENIGN (n= 39)		MALIGNANT (n=27)	
	Mean	SD	Mean	SD
Mean Radius (µm)	11.7852 ±	2.0901	11.7714 ±	1.7073
MeanTexture	17.2192 ±	4.285	27.7285 ±	9.7497
Mean Perimeter (µm)	76.3515 ±	14.0874	78.0541 ±	12.3022
Mean Area (µm²)	455.4103 ±	196.6025	434.4111 ±	128.6403
Mean Smoothness	0.1043 ±	0.0163	0.1192 ±	0.015
Mean Compactness	0.1045 ±	0.0567	0.174 ±	0.0733
Mean Concavity	0.0888 ±	0.0599	0.1217 ±	0.0593
Mean Concave Points	0.043 ±	0.027	0.0668 ±	0.0322
Mean Symmetry	0.2012 ±	0.0292	0.223 ±	0.0287
Mean Fractal Dimension	0.067 ±	0.0077	0.0756 ±	0.0079
SE Radius (µm)	0.5237 ±	0.4828	0.4137 ±	0.1327
SE Texture	0.7324 ±	0.3421	1.7877 ±	0.9776
SE Perimeter (µm)	3.6096 ±	3.3335	3.0572 ±	0.967
SE Area (µm2)	45.431 ±	55.4046	31.3467 ±	14.1543
SE Smoothness	0.008 ±	0.0018	0.0064 ±	0.0013
SE Compactness	0.027 ±	0.0183	0.0314 ±	0.0096
SE Concavity	0.0347 ±	0.0246	0.0313 ±	0.0098
SE Concave Points	0.0115 ±	0.0053	0.012 ±	0.0024
SE Symmetry	0.0208 ±	0.0058	0.0194 ±	0.0029
SE Fractal Dimension	0.0041 ±	0.0019	0.0041 ±	0.0009
Extreme Value - Radius (µm)	15.0115 ±	3.6484	15.6822 ±	2.5923
Extreme Value - Texture	22.4664 ±	5.6151	43.6733 ±	16.6618
Extreme Value - Perimeter (µm)	99.2349 ±	25.3583	106.9496 ±	19.1705
Extreme Value - Area (µm2)	733.2897 ±	422.0634	751.1593 ±	257.0683
Extreme Value - Smoothness	0.1678 ±	0.0226	0.1744 ±	0.0217
Extreme Value - Compactness	0.3437 ±	0.2065	0.5158 ±	0.168
Extreme Value - Concavity	0.3827 ±	0.2109	0.4741 ±	0.1549
Extreme Value - Concave Points	0.1375 ±	0.0445	0.1843 ±	0.0406
Extreme Value - Symmetry	0.3642 ±	0.065	0.4047 ±	0.0611
Extreme Value - Fractal Dimension	0.1033 ±	0.0225	0.1191 ±	0.0175

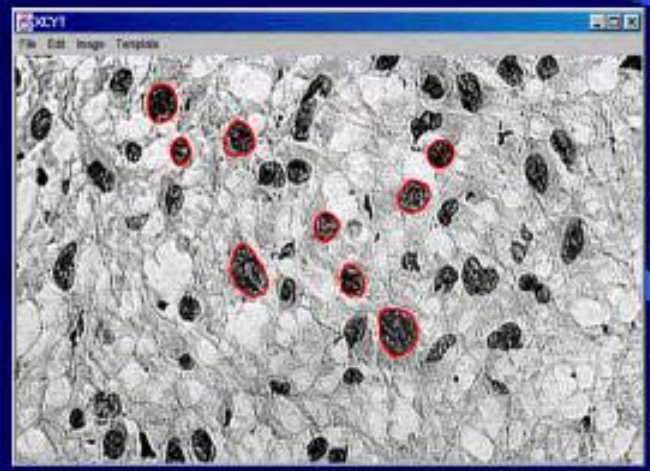
Note: SE = standard error; SD = standard deviation

Inductive Machine Learning

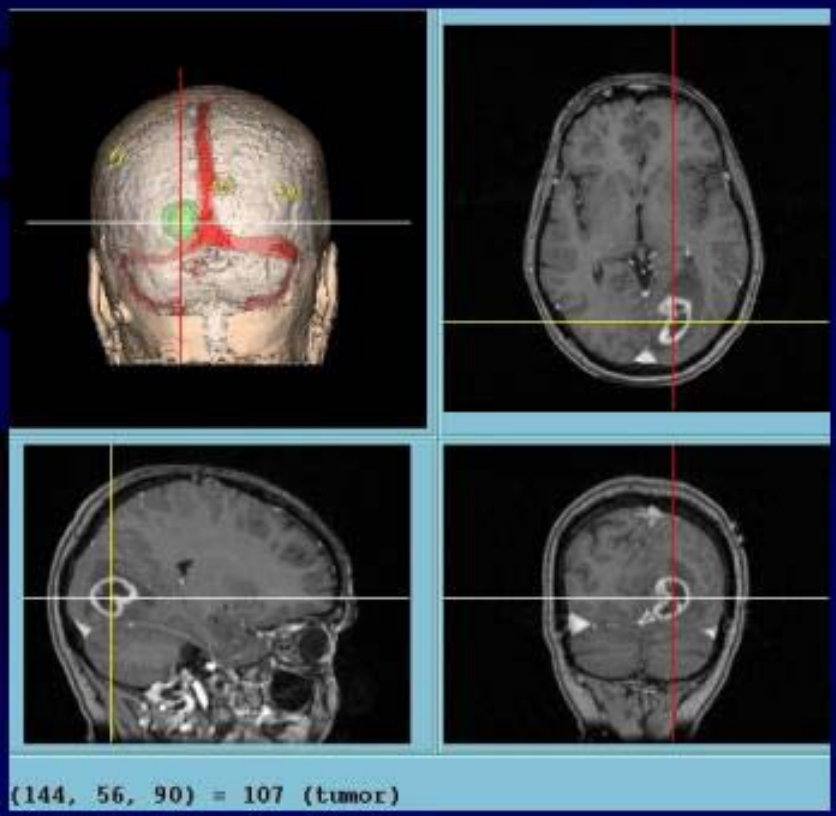
- Classification procedure uses linear programming
- Decision tree model to categorize new cases
- Accuracy determined by 10-fold cross-validation

"Malignancy" Index

- Limited training data set
- Total 66 samples
- 27 glioblastoma specimens
- 39 normal brain specimens
- Accuracy using Xcyt program was 92.4%



Digital Analysis of Radiographic Images

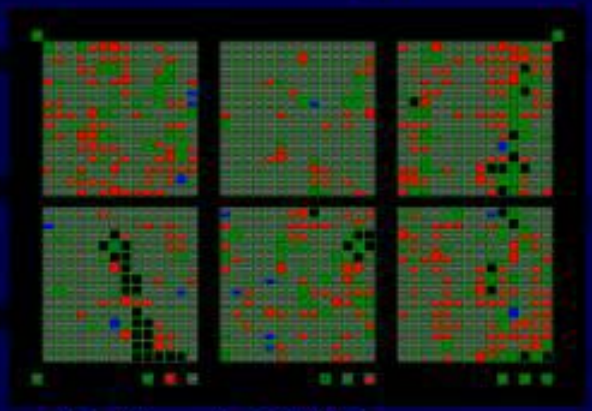


Create "smart software" - resulting in a searchable archive to assist in analysis

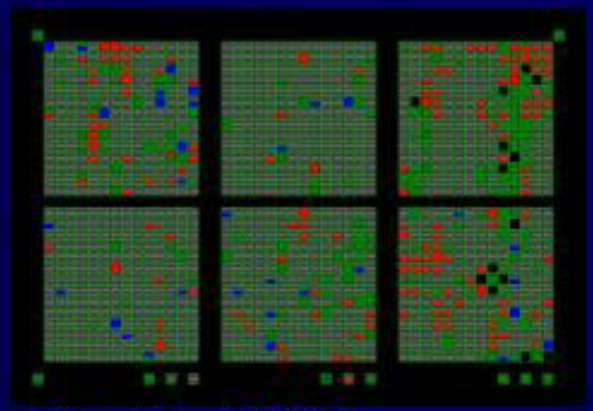
Diagnosis

Prognosis

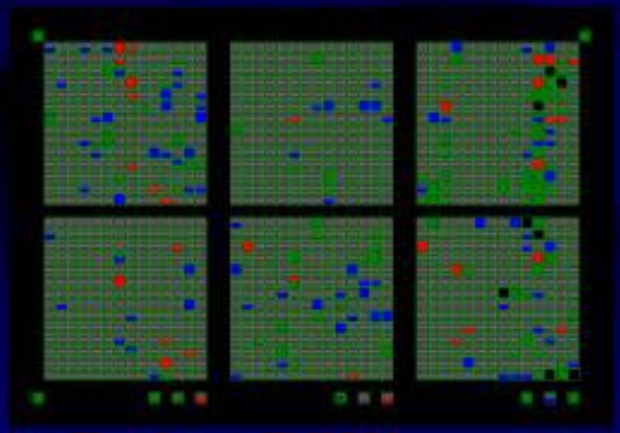
Comparison of Multiple Patients all with Pathologic Diagnosis of Glioblastoma



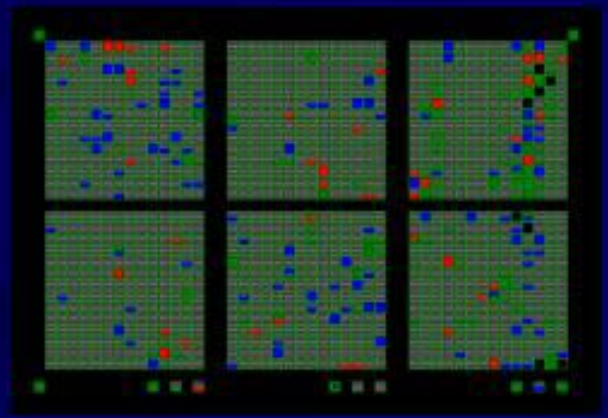
Patient GSR



Patient RSC



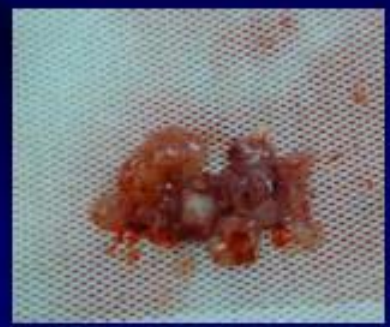
Patient TCW

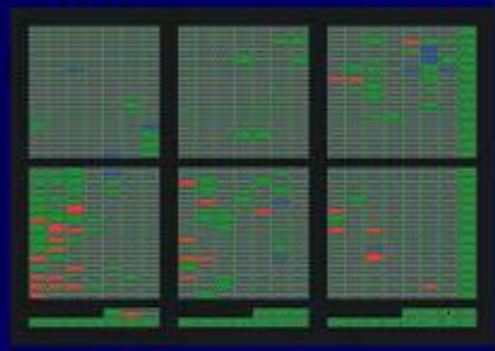


Patient KJE

Analysis of Digital Pathologic Diagnosis and Genetic Transcription Profiles in Patients with Malignant Glioma treated with Implantable BCNU

- 25 patients with malignant glioma
- Implanted with BCNU polymer
- Tumor tissue cultured and genetic transcription profile obtained
- Goal is to identify any trends in tumor response linked with gene expression
- Special interest in those undergoing reoperation





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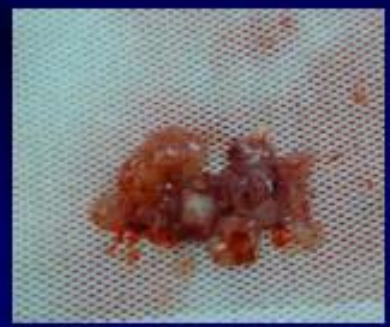
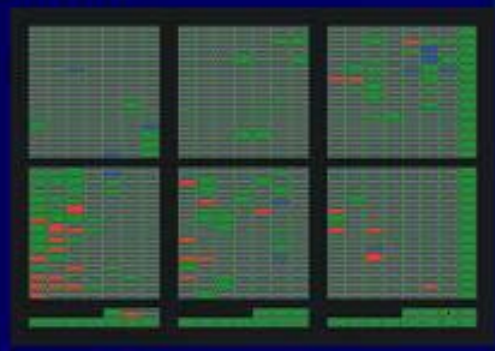
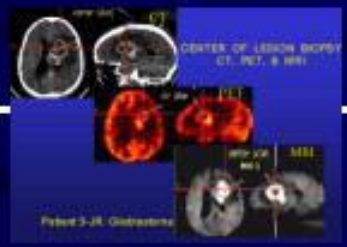




Patient presents with CNS disease

Prediction of response to therapy or clinical outcome

Multimodality Neuroimaging



Diagnosis

"Tailored" Diagnostic Procedure Computer Enhanced

Molecular Pathological Diagnosis

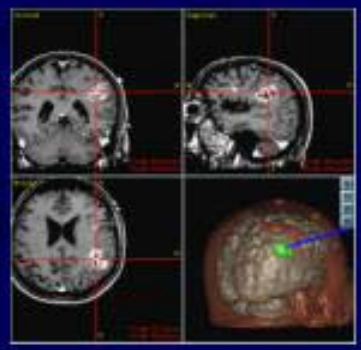
Treatment Based on Advanced Molecular Diagnostics

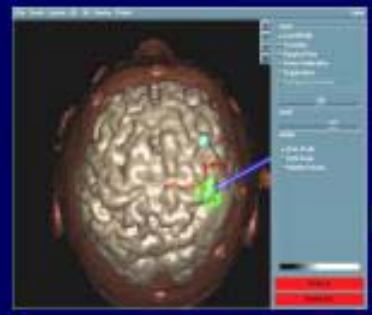
Delivery

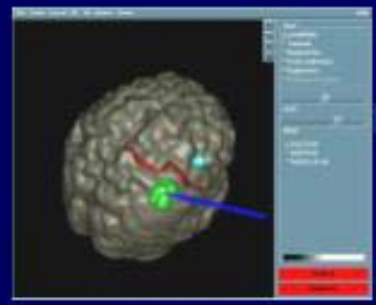
2010 ??

Delivery

- Image guided surgery
- Stereotactic radiosurgery
- Brachytherapy
- Local drug delivery
  - Polymeric delivery
  - Infusion
- Subselective arterial delivery







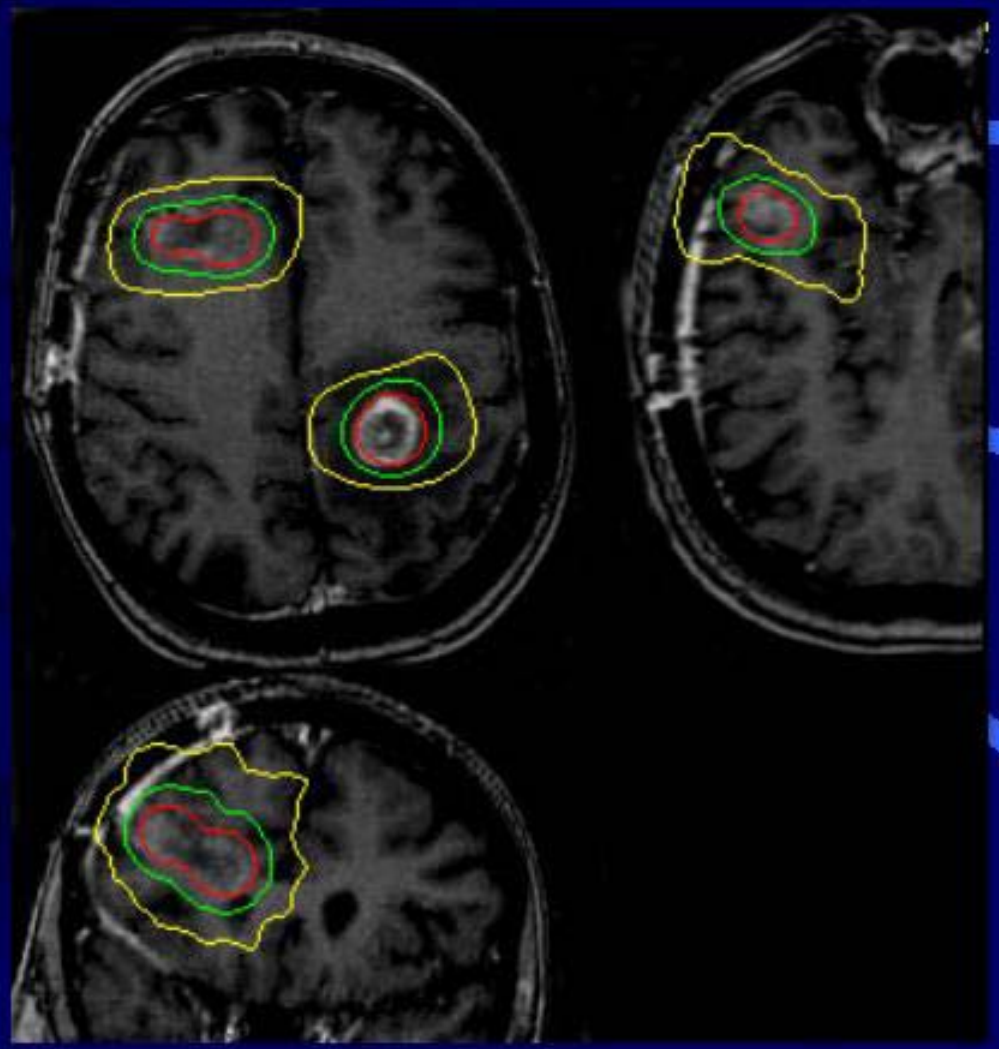
Stereotactic Radiosurgery

Framed

Frameless

Cranial

Extracranial



Gliasite – Brachytherapy Catheter

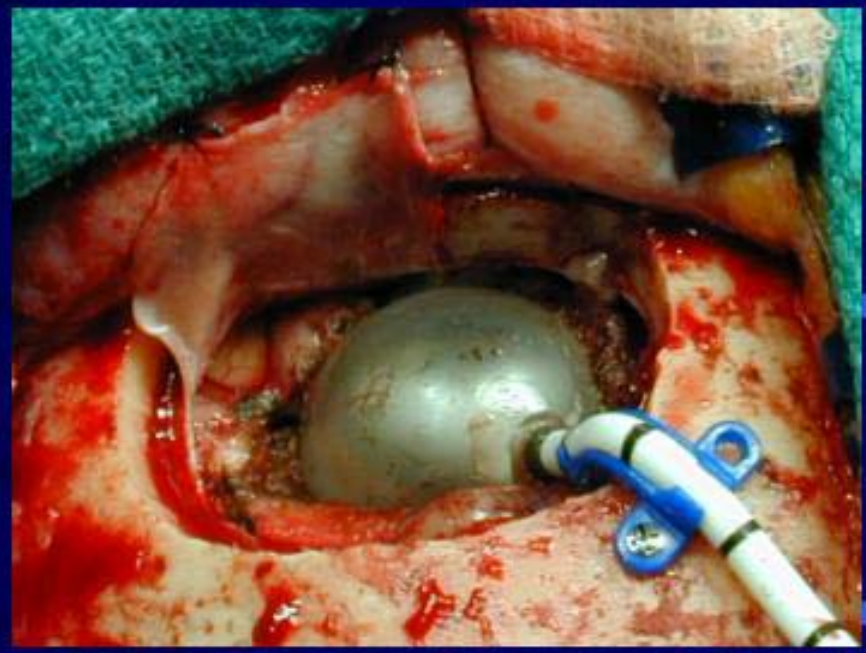
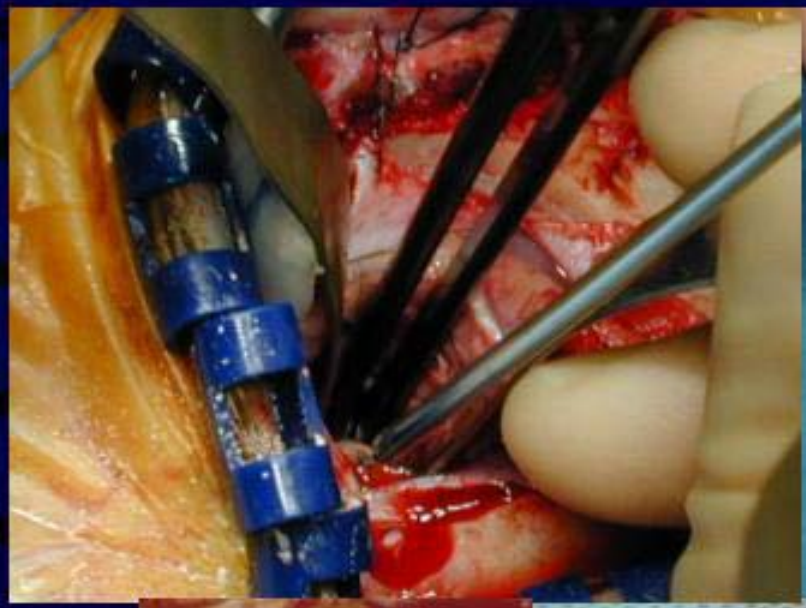
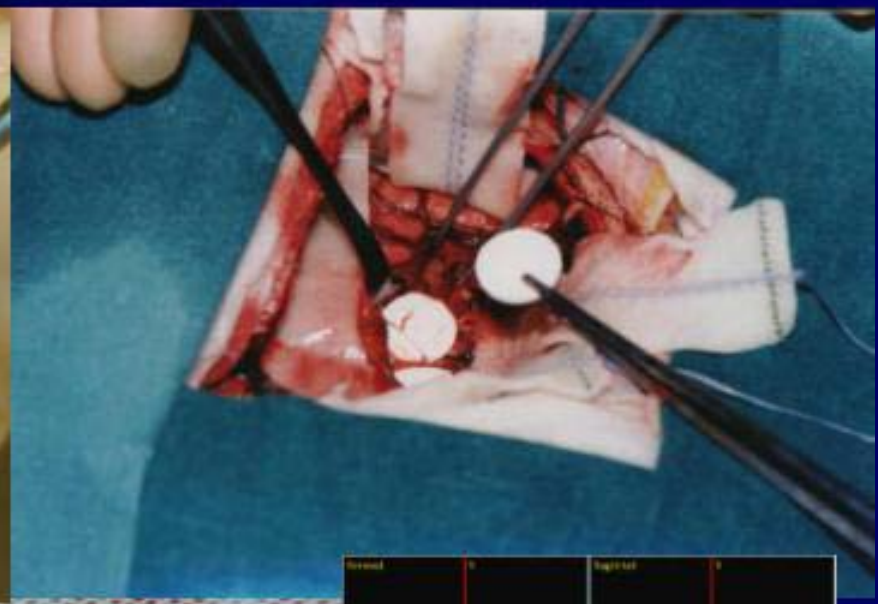
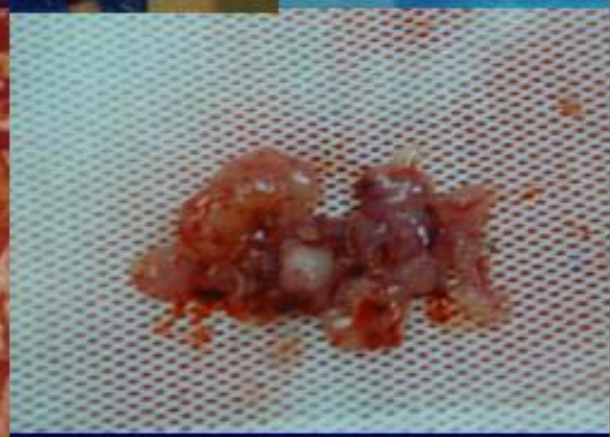


Image Guided Craniotomy: Debulking and Implants







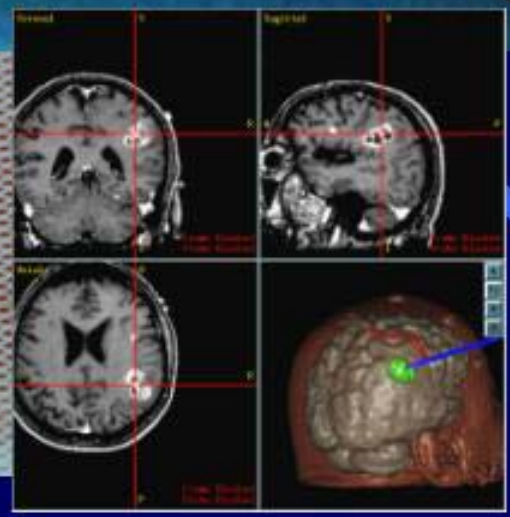
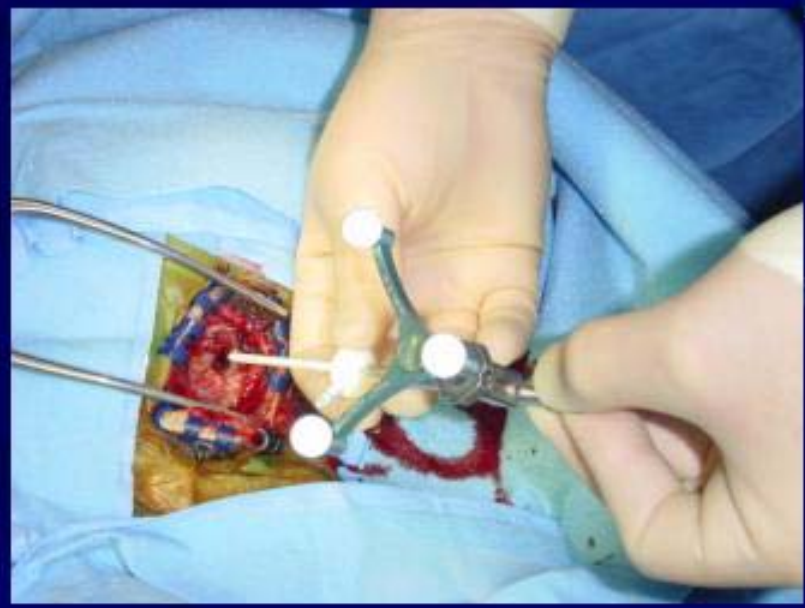


Image Guided Therapy

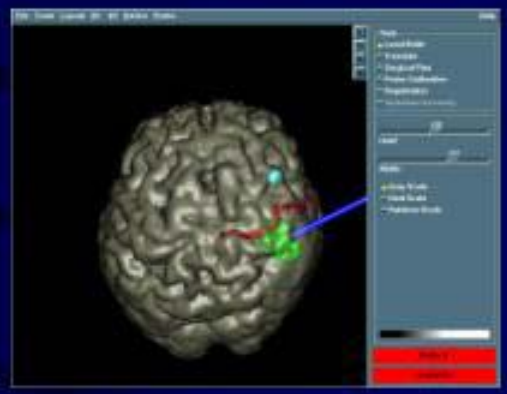
Equipment modification for real-time tracking

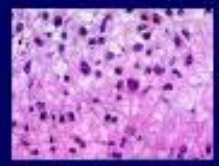


Direct Cranial Fixation for Image Guidance – Awake Craniotomy

Delivery of Genetic Material to the Central Nervous System

Image Guidance





Macroscopic delivery

- Injection
- Infusion
- Particle delivery
- Regional electroporation

Site Specific Delivery

Cellular level (transfection

- Vectors
- Cell-mediated
- Effectors
- Promoters
- Transcription factors
- Immunomodulation

Treatment of CNS Disease:

Gene replacement

Polymeric delivery

Growth factor inhibitors

Viral vectors

Immuno-modulation

Anti-sense vectors

Apoptosis agents

Biological inhibitors

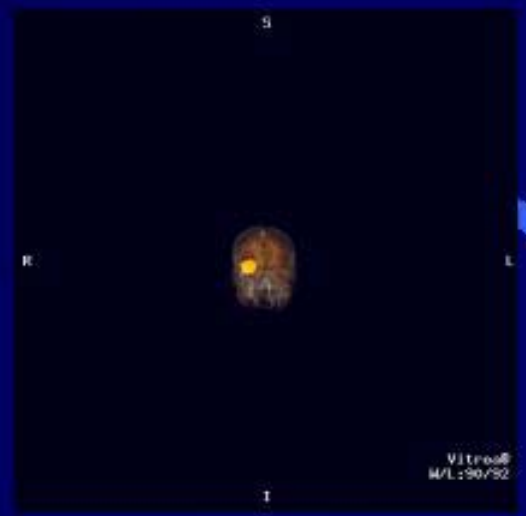
Cell implants

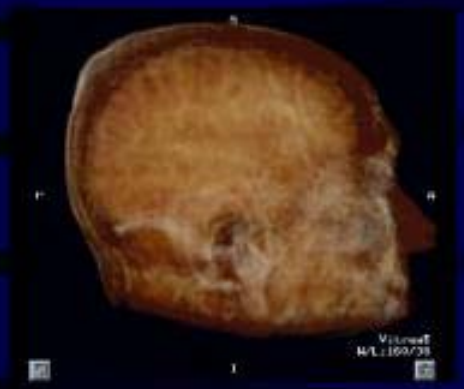
Neurosurgery

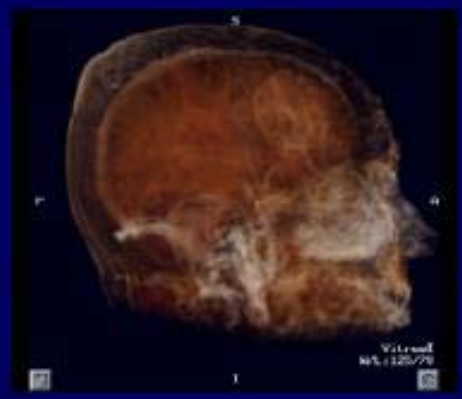
Image Guidance

Treatment

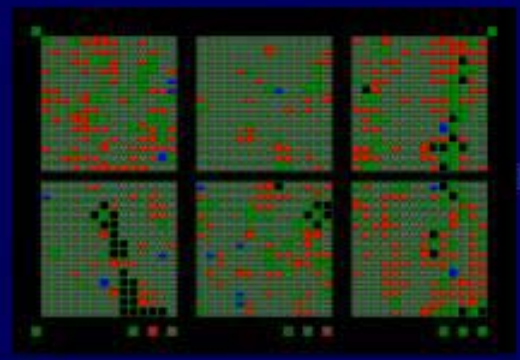
Targetted CNS Delivery

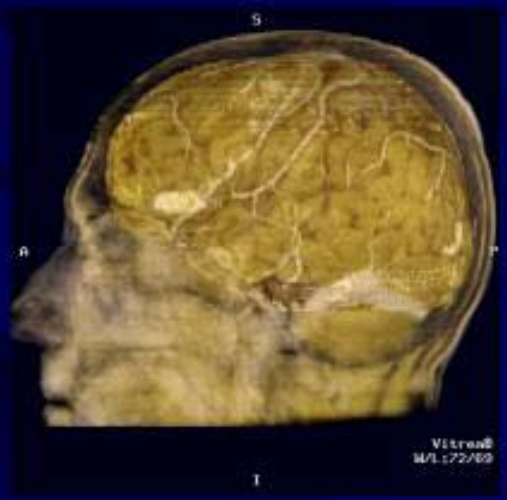


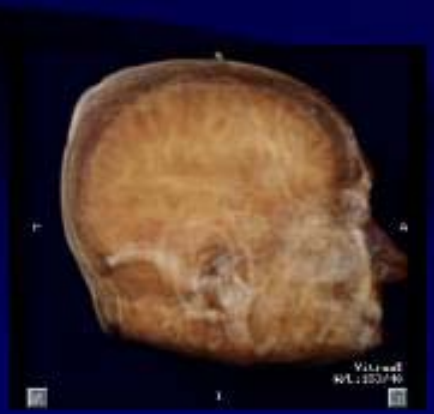
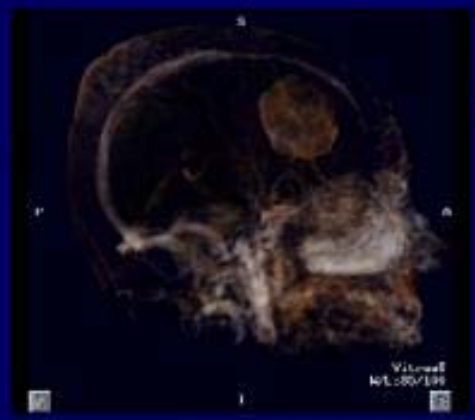




2084 ?







Thank you.